

Higher Serum Alanine Transaminase Levels in Male Urokinase-Type Plasminogen Activator-Transgenic Mice Are Associated With Improved Engraftment of Hepatocytes but not Liver Sinusoidal Endothelial Cells.

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Authors: Marina E Fomin, Ashley I Beyer, Jean Publicover, Kai Lu, Sonia Bakkour, Graham Simmons, Marcus O Muench

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Funding Grants: Modulating Liver Sinusoidal Endothelial Cell Permeability to Enhance Engraftment of Endothelial Cell Progenitors for the Treatment of Hemophilia A

Public Summary:

The effect of sex on disease and treatment outcome is an important parameter in biomedical research. We evaluated the effect of sex in a rodent model of liver damage and discovered that male mice had higher levels of liver damage than female mice based on a commonly used blood test that measures liver damage. The liver enzyme serum alanine transaminase was found to be at higher levels in male mice than female mice. We next evaluated the effects of greater liver damage on our ability to transplant human cells into the livers of male and female mice. As anticipated, higher levels of hepatocyte engraftment were observed, on average, in male mice than female mice, confirming that the degree of liver damage directly affects the ability of transplanted hepatocytes to engraft the liver. We evaluated two other cell types as well, blood progenitors and liver sinusoidal endothelial cells (LSECs). The modest differences in liver damage between male and female mice did not affect the engraftment of blood stem cells or LSECs. The engraftment of LSECs was of particular interest to our project as these cells are the source of factor VIII, the clotting factor affected in hemophilia A patients. We have previously observed robust engraftment of LSECs in our mice with liver disease. The findings that modest differences in the degree of hepatocyte damage in these mice do not noticeably affect the degree of LSEC engraftment point to a threshold effect in how hepatocyte damage affects LSECs engraftment. These findings help us to better understand how hepatocyte damage affects the engraftment of LSECs in our mouse model. Understanding the mechanism of LSEC engraftment in this model may help us to design methods of LSEC transplantation to treat hemophilia A.

Scientific Abstract:

The effects of sex on the degree of liver damage and human cell engraftment were investigated in immunodeficient urokinase-type plasminogen activator-transgenic (uPA-NOG) mice. Liver damage, measured by serum alanine transaminase (ALT) levels, was compared in male and female uPA-NOG mice of different ages. Male mice had significantly higher ALT levels than females with a median of 334 versus 158 U/L in transgenic homozygous mice, respectively. Mice were transplanted with human adult hepatocytes or fetal liver cells and analyzed for any correlation of engraftment of hepatocytes, liver sinusoidal endothelial cells (LSECs), and hematopoietic cells with the degree of liver damage. Hepatocyte engraftment was measured by human albumin levels in the mouse serum. Higher ALT levels correlated with higher hepatocyte engraftment, resulting in albumin levels in male mice that were 9.6 times higher than in females. LSEC and hematopoietic cell engraftment were measured by flow cytometric analysis of the mouse liver and bone marrow. LSEC and hematopoietic engraftment did not differ between male and female transplant recipients. Thus, the sex of uPA-NOG mice affects the degree of liver damage, which is reflected in the levels of human hepatocyte engraftment. However, the high levels of LSEC engraftment observed in uPA-NOG mice are not further improved among male mice, suggesting that a lower threshold of liver damage is sufficient to enhance endothelial cell engraftment. Previously described sex differences in human hematopoietic stem cell engraftment in immunodeficient mice were not observed in this model.

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